IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

TWINSTRAND BIOSCIENCES, INC., & UNIVERSITY OF WASHINGTON, Plaintiffs, v. GUARDANT HEALTH, INC., Defendant.	C.A. No. _____ **JURY TRIAL DEMANDED**

COMPLAINT

Plaintiffs TwinStrand Biosciences, Inc. ("TwinStrand") and University of Washington ("UW") file this Complaint against Defendant Guardant Health, Inc. ("Guardant"), alleging as follows:

NATURE OF THE ACTION

1. This is an action for infringement of U.S. Patent Nos. 10,287,631 ("the '631 patent"); 10,689,699 ("the '699 patent"); 10,752,951 ("the '951 patent"); and 10,760,127 ("the '127 patent") (collectively, "the Asserted Patents") arising under the patent laws of the United States, 35 U.S.C. § 1 *et seq.* Guardant has infringed and continues to infringe the claims of the Asserted Patents by using, offering for sale, and selling its genetic-sequencing services in the United States.

PARTIES

2. TwinStrand is a corporation organized and existing under the laws of the State of Delaware and having its principal place of business at 3131 Elliott Ave., Suite 750, Seattle, WA, 98121. At all relevant times, TwinStrand has been the exclusive licensee of the Asserted Patents.

3. UW is a public institution of higher education and an agency of the State of Washington. Its principal place of business is in the city of Seattle, Washington. At all relevant times, UW has owned all right, title, and interest in the Asserted Patents.

4. Guardant is a corporation organized and existing under the laws of the State of Delaware and having its principal place of business at 505 Penobscot Dr., Redwood City, CA 94063.

JURISDICTION AND VENUE

5. This action arises under the patent laws of the United States, 35 U.S.C. §§ 1, *et seq*., and this Court has jurisdiction over the subject matter of Plaintiffs' claims pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

6. This Court has jurisdiction over Guardant at least because Guardant is a Delaware corporation.

7. This Court also has jurisdiction over Guardant because Guardant has purposefully availed itself of the rights and benefits of Delaware law by engaging in systematic and continuous contacts with Delaware, including by Guardant selling and offering for sale its infringing genetic-sequencing products in Delaware.

8. Venue is proper in this District pursuant to 28 U.S.C. § 1400(b) because Guardant resides in Delaware as a consequence of its incorporation in the state.

THE PATENTS-IN-SUIT

9. On May 14, 2019, the United States Patent and Trademark Office lawfully issued the '631 patent, entitled "Methods of Lowering the Error Rate of Massively Parallel DNA Sequencing Using Duplex Consensus Sequencing." A true and correct copy of the '631 patent is attached hereto as Exhibit A.

10. On June 23, 2020, the United States Patent and Trademark Office lawfully issued the '699 patent, entitled "Methods of Lowering the Error Rate of Massively Parallel DNA Sequencing Using Duplex Consensus Sequencing." A true and correct copy of the '699 patent is attached hereto as Exhibit B.

11. On August 25, 2020, the United States Patent and Trademark Office lawfully issued the '951 patent, entitled "Methods of Lowering the Error Rate of Massively Parallel DNA Sequencing Using Duplex Consensus Sequencing." A true and correct copy of the '951 patent is attached hereto as Exhibit C.

12. On September 1, 2020, the United States Patent and Trademark Office lawfully issued the '127 patent, entitled "Methods of Lowering the Error Rate of Massively Parallel DNA Sequencing Using Duplex Consensus Sequencing." A true and correct copy of the '127 patent is attached hereto as Exhibit D.

BACKGROUND

13. The Asserted Patents cover groundbreaking duplex sequencing methods invented at UW by Jesse Salk, M.D., Ph.D., then a medical student, and two of his academic colleagues. Among many other applications, these duplex sequencing methods, for the first time, allowed for reliable, early, non-invasive cancer detection and post-treatment cancer monitoring in patients simply by analyzing blood plasma, without the need for biopsies of solid tumors. The inventions of the Asserted Patents can detect mutations in DNA target molecules that are present in extremely low abundance relative to the DNA from healthy cells—an elusive feat that previous sequencing methods could not achieve. The inventions of the Asserted Patents overcome the shortcomings in the prior art, offering unprecedented accuracy without sacrificing the high throughput of modern DNA sequencing approaches.

14. Following their invention, Dr. Salk and his co-inventors founded TwinStrand to make their inventions available to clinicians and researchers. TwinStrand exclusively licenses the Asserted Patents from UW and practices Duplex Sequencing through its sale of kits and services under its TwinStrand Duplex Sequencing™ technology platform.

A. The Need for High-Accuracy, High-Throughput Sequencing Methods

15. Genetic mutations are the hallmark of cancer and other significant diseases affecting human health. Detecting the presence of these mutations in an individual was thought to be a promising way to screen for or diagnose cancers and other illness before individuals became symptomatic. But, in many instances, these hallmark genetic mutations are at an ultra-low frequency relative to the presence of DNA from healthy cells in a given sample, requiring the use of highly sensitive and specific genetic methods that did not exist before the inventions of the Asserted Patents.

16. Conventional genetic-sequencing methods generally involve trade-offs among accuracy, throughput, and expense. For example, the Sanger sequencing method allowed scientists to complete the Human Genome Project, but that effort took decades and cost many millions of dollars. Sanger sequencing's low throughput and high expense make it unsuitable for many applications. Moreover, Sanger sequencing approaches simply report the average sequence of a collection of many grouped molecules, obscuring low frequency mutations.

17. Next Generation Sequencing ("NGS") approaches sequence millions of individual DNA molecules at a time and offer much higher throughput at a fraction of the cost per DNA base compared to Sanger sequencing. But, conventional NGS approaches are still notoriously inaccurate. Indeed, conventional NGS approaches generate error rates of 0.1%–1%—meaning up to one in one hundred DNA bases are miscalled, and the presence of real biological mutations are obscured.

18. For many applications, the existing sequencing methods offered by Sanger and conventional NGS approaches were adequate. But before Dr. Salk's inventions, neither could be used effectively in applications where the target DNA is at an ultra-low frequency, as is the case with early cancer detection using blood plasma or when looking for residual disease in a patient following a treatment course. Indeed, DNA from cancer cells is only present in blood plasma in extremely low concentrations; the overwhelming majority of DNA present comes from non-cancerous cells. To detect a target cancer mutation in that case, a sequencing method was needed that achieves high throughput *and* high sensitivity—something that conventional approaches simply could not deliver.

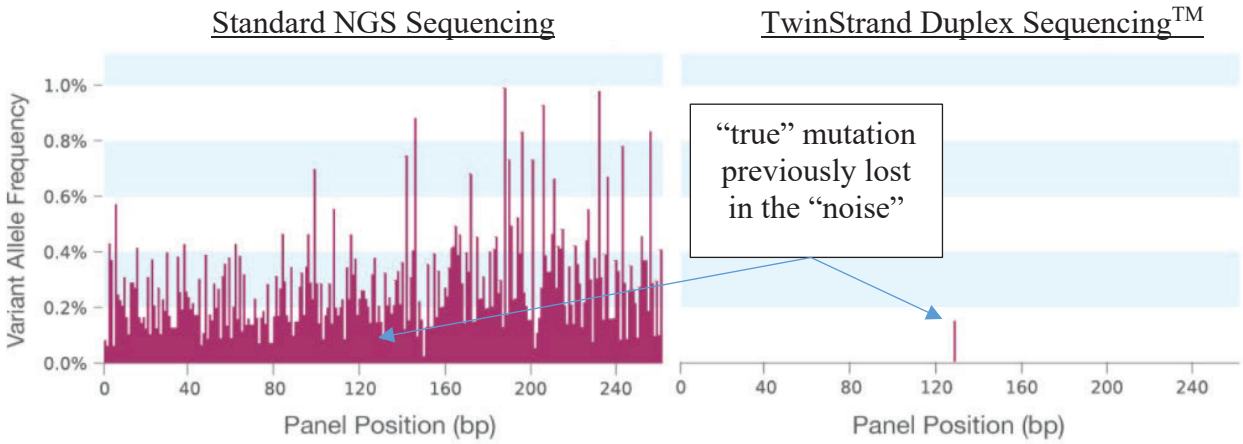
B. The Inventions

19. While at UW, Dr. Salk, then a medical student, and his colleagues invented breakthrough sequencing methods that achieved a 10,000-fold increase in accuracy over standard NGS approaches, without sacrificing throughput, eliminating nearly all technical errors introduced by NGS sequencing.

20. These new sequencing inventions avoid the errors inherent in conventional NGS approaches by leveraging the duplicated information stored in each complementary strand of DNA. By labeling each original double-stranded target molecule, Dr. Salk and his team found that they could track each sequenced strand back to its original template molecule. And, by separately and uniquely labeling each complementary strand of that molecule, one strand of each molecule could be differentiated from the other strand of that molecule. This innovative labelling strategy allows for the comparison of complementary strands of the original target molecule. Because true mutations in a molecule are duplicated on both complementary strands, this comparison allows true mutations to be distinguished from sequencing errors, which occur on only one strand. Free of the performance trade-offs of prior sequencing approaches, Dr. Salk and

his co-inventors' novel TwinStrand Duplex Sequencing™ methods, claimed in the UW patents, enable the identification of rare genetic mutations that have very low frequencies among a population of target DNA molecules.

21. The Duplex Sequencing methods conceived by Dr. Salk and his co-inventors eliminate essentially all of the background noise generated by sequencing errors in prior-art NGS sequencing methods—allowing for accurate identification of mutations that are present at an ultra-low frequency. The charts below compare the same gene sequenced with standard NGS sequencing with TwinStrand Duplex Sequencing™ technology. With standard NGS sequencing, every position in the sequenced gene appears mutated in 0.1 to 1% of the molecules sequenced. In contrast, UW's patented methods, embodied by the TwinStrand Duplex Sequencing™ technology, remove this NGS noise to reveal the previously hidden, low-frequency true mutation.



TwinStrand Biosciences, "TwinStrand Duplex Sequencing™" technology brochure (2020) (Exhibit E).

22. TwinStrand's technology—built on the inventions of the Asserted Patents—uniquely provides the sensitivity and specificity necessary for accurate cancer detection and monitoring with non-invasive blood draws—liquid biopsies—resulting in dramatic

improvements in oncology patient care. By using UW's patented Duplex Sequencing methods, the risk to the diagnostic patient is lower, cancer can be detected earlier (sometimes even before a tumor mass is identified), optimal treatments can be identified and prescribed quickly, and the costs to the patient and healthcare system are significantly reduced while personalized care improves health outcomes. Additionally, with much greater sensitivity, recurrent or residual cancer can be detected at previously undetectable levels to allow medical intervention at stages when they are most effective.

23. For patients undergoing cancer treatment, the inventions can detect the emergence of drug-resistant cancer cells, allowing clinicians to select appropriate therapeutics.

24. In addition to cancer applications, the patented technology offers the ability to aid in crime-scene forensics, to identify the emergence of drug-resistant microbes, and to sequence fetal DNA from maternal blood for non-invasive prenatal diagnostics, to name just a few applications.

25. Realizing the enormous value of their breakthrough, the inventors, in collaboration with UW, sought patent protection for their inventions starting in early 2012. And in 2015, Dr. Salk and his colleagues co-founded TwinStrand with a Small Business Innovation Research grant and seed funding to develop and commercialize the patented duplex sequencing methods.

26. Today, TwinStrand applies the patented duplex sequencing methods to applications in clinical medicine and life sciences, among others. TwinStrand's customers include researchers, academic institutions, government and private laboratories, federal agencies, health systems, regulatory bodies, pharma and biotech companies, and others, whose work benefits from highly accurate sequencing techniques. TwinStrand provides services for nucleic

acid analysis using the patented Duplex Sequencing methods and provides customers with Duplex Sequencing kits. These kits include a DNA library prep kit containing the reagents, adapters, and other components necessary to practice its Duplex Sequencing process. TwinStrand also provides access to bioinformatics software to process raw sequence read files and produce error-corrected sequences according to the patented processes.

C. Guardant's Willful Infringement of the Asserted Patents

1. Guardant's infringing products and services

27. Starting in 2014, Guardant began selling a number of products and services to monetize a Guardant-performed sequencing method that infringes the Asserted Patents. Guardant markets this sequencing method under the moniker "Digital Sequencing Technology." Guardant IPO Prospectus, 96, 105, 108, and 120 (2018) ("Guardant IPO Prospectus") (Exhibit F).

28. In particular, Guardant sells kits for diagnostic purposes to customers around the world, including the Guardant360 lab developed test ("LDT"), Guardant360 CDx ("CDx"), GuardantOMNI ("Omni"), Guardant Reveal[1] ("Reveal"), Guardant LUNAR-2 ("LUNAR-2"), Guardant360 Response, and Guardant360 TissueNext (collectively, "the Guardant Kits" or "Accused Products"). The Guardant Kits are used by Guardant's customers to collect tissue samples and return them to Guardant. Guardant then performs its infringing sequencing method at its Redwood City, California laboratory. Each of these kits uses the same or essentially the same underlying sequencing technology, which Guardant calls its Digital Sequencing Technology. *Solutions*, GUARDANT HEALTH, https://guardanthealth.com/solutions/ (last visited Aug. 2, 2021) (Exhibit G).

[1] Guardant previously marketed "Reveal" as the "LUNAR-1" test.

29. In 2017, Dr. Rick Lanman, Guardant's Chief Medical Officer at the time, described the methods that Guardant performs, stating: "We actually barcode. You have double stranded DNA—two strands. Each one is going to get a digital bar code attached to it. After we sequence it, if those two strands don't match—the Watson allele and Crick allele, they should be complementary—then we correct it." The Lung Cancer Living Room – Molecular Testing, Bonnie J. Addario Lung Cancer Foundation, YOUTUBE, 0:56:12–0:56:36 (Feb. 21, 2017).

30. Guardant further monetizes its infringing sequencing method by selling certain data services, including Guardant Connect and Guardant Inform (collectively, "the Guardant Services" or "Accused Services"), to its customers. With Guardant Connect, Guardant sells access to a real-time database of patients receiving Guardant360 liquid biopsy assays so that customers can identify patients who may be eligible for clinical trials. And, with Guardant Inform, Guardant sells access to clinical information and genomic data collected from Guardant's infringing Guardant360 liquid biopsy test.

2. Guardant knew or should have known of the Asserted Patents and that its conduct amounted to infringement

31. Guardant undoubtedly knew or should have known of the inventions claimed in each of the Asserted Patents before it launched the Accused Products. At or around the time Guardant launched the first of the Accused Products, Guardant made several unsuccessful attempts to license the patent family that includes the Asserted Patents. Having failed there, Guardant attempted and failed to cancel the exclusive license between UW and TwinStrand. And, Guardant repeatedly faced patentability rejections based on UW's patent documents when Guardant was prosecuting its own patent applications directed to its infringing commercial sequencing method.

32. Indeed, on numerous occasions, Guardant cited the Asserted Patents during Guardant's prosecution of its own later-filed patents attempting to cover its infringing technology.[2] For example, in a non-final rejection of one of Guardant's applications, the Examiner considered the '631 patent to be one of three "references of interest."[3] In another instance, the Examiner rejected Guardant's application as anticipated by a UW application from which the asserted '631 and '699 patents were continuations.[4]

33. In *inter partes* review proceedings, a petitioner challenged the validity of Guardant's genetic sequencing patents using as prior-art references a provisional application to which the Asserted Patents claim priority and a patent family member of the Asserted Patents.[5]

34. In European opposition proceedings, UW's PCT application 2013/032665—whose national stage application yielded the '631, '699, and '951 patents—was cited to revoke Guardant's European Patent Nos. 3087204, 3378952, and 2893040, which all related to genetic sequencing.

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[2] U.S. Patent App. Nos. 16/593,633 (Non-Final Rejection and Notice of References Cited dated January 22, 2020), 15/669,779 (IDS dated April 27, 2020), 16/389,680 (IDS dated April 16, 2020), 16/601,168 (IDS dated June 3, 2020 and IDS dated July 13, 2020), 16/897,038 (IDS dated June 25, 2020 and July 28, 2020), and 17/068,710 (IDS dated October 12, 2020 and November 23, 2020).

[3] U.S. Patent App. No. 16/593,633 (Non-Final Rejection and Notice of References Cited dated January 22, 2020).

[4] U.S. Patent App. No. 14/712,754 (Non-Final Office Action dated December 4, 2015).

[5] *See, e.g.*, *Found. Med., Inc., v. Guardant Health, Inc.,* PTAB-IPR2019-00130, Patent Owner's Preliminary Response, at 12–14 (March 6, 2019) (citing U.S. Patent No. 9,752,188); *Found. Med., Inc., v. Guardant Health, Inc.,* PTAB-IPR2019-00653, Petition for *Inter Partes* Review, at Exhibits 1011 and 1012 (May 20, 2019) (citing U.S. Patent No. 9,752,188 and U.S. Provisional App. 61/613,413).

35. Yet, despite facing TwinStrand's licensed intellectual property time and again, Guardant continued its infringing activities in conscious disregard of UW and TwinStrand's intellectual property rights. Guardant's infringement has gone on long enough.

COUNT I

(Direct Infringement of U.S. Patent No. 10,287,631)

36. Plaintiffs re-allege and incorporate by reference Paragraphs 1–35 above, as if fully set forth herein.

37. The '631 patent is directed to methods of generating high accuracy sequence reads of a population of double-stranded target nucleic acid molecules. Claim 1 of the patent recites:

> A method of generating high accuracy sequence reads of a population of double-stranded target nucleic acid molecules, comprising:
>
> ligating each of the double-stranded target nucleic acid molecules to at least one adapter molecule, to form a population of adapter-target nucleic acid complexes, wherein each of the adapter molecules comprises—
>
> (a) a degenerate or semi-degenerate single molecule identifier (SMI) sequence that alone or in combination with the target nucleic acid fragment ends uniquely labels each ligated double-stranded target nucleic acid molecule such that each ligated double-stranded target nucleic acid molecule is distinguishable from other ligated double-stranded target nucleic acid molecules in the population, and
>
> (b) a strand-distinguishing nucleotide sequence that, following the ligation step, provides a region of non-complementarity between a first strand of each adapter-target nucleic acid complex and a second strand of the same adapter-target nucleic acid complex;
>
> for each of the adapter-target nucleic acid complexes—
>
> amplifying each strand of the adapter-target nucleic acid complex to produce a plurality of first strand adapter-target nucleic acid complex amplicons and a plurality of second strand adapter-target nucleic acid complex amplicons;

sequencing the adapter-target nucleic acid complex amplicons to produce a plurality of first strand sequence reads and plurality of second strand sequence reads;

grouping the first strand sequence reads and the second strand sequence reads into a family of first and second strand sequence reads based on the degenerate or semi-degenerate SMI sequence alone or in combination with the target nucleic acid fragment ends;

separating the first and second strand sequence reads into a set of first strand sequence reads and a set of second strand sequence reads based on the region of non-complementarity between the first strand and the second strand of the adapter-target nucleic acid complex;

confirming the presence of at least one first strand sequence read and at least one second strand sequence read;

comparing the at least one first strand sequence read with the at least one second strand sequence read;

identifying nucleotide positions where the compared first and second strand sequence reads are non-complementary;

identifying nucleotide positions where the compared first and second strand sequence reads are complementary; and

generating a high accuracy consensus sequence read for each of the double-stranded target nucleic acid molecules in the population that includes only the nucleotide positions where the compared first and second strand sequence reads are complementary.

38. Guardant has infringed and continues to infringe at least claim 1 of the ’631 patent, literally or under the doctrine of equivalents, by performing the methods of the ’631 patent in the United States.

39. Guardant practices the preamble of claim 1 of the ’631 patent, which provides “[a] method of generating high accuracy sequence reads of a population of double-stranded target nucleic acid molecules.” For example, Guardant touts that its sequencing method provides highly accurate reads of double-stranded DNA molecules. The Guardant360 Assay Specifications, at 1 (2018) (Exhibit H); *see also* Guardant IPO Prospectus at 121.

40. Guardant also practices the "ligating" step of claim 1 of the '631 patent. This element recites "ligating each of the double-stranded target nucleic acid molecules to at least one adapter molecule, to form a population of adapter-target nucleic acid complexes." Guardant practices this element by at least "repair[ing] ends of DNA with a 5' phosphate prior to ligation of adapters." Richard Lanman, et al., *Analytical and Clinical Validation of a Digital Sequencing Panel for Qualitative, Highly Accurate Evaluation of Cell-Free Circulating Tumor DNA*, 10 PLOS ONE 10, at 18 (Oct. 16, 2015) ("Lanman") (Exhibit I) (article authored by Guardant employees regarding Guardant's digital sequencing technology). Guardant at least uses "blunt-end ligation" to attach library adapters to the ends of fragments of cell-free DNA. FDA Summary of Safety and Effectiveness Data for Premarket Approval No. P200010, at 6 (Feb. 10, 2020) ("FDA Summary No. P200010B") (Exhibit J) (FDA summary of data for Guardant360 CDx product).

41. Guardant also practices the "SMI sequence" element of claim 1 of the '631 patent. This element recites "a degenerate or semi-degenerate single molecule identifier (SMI) sequence that alone or in combination with the target nucleic acid fragment ends uniquely labels each ligated double-stranded target nucleic acid molecule such that each ligated double-stranded target nucleic acid molecule is distinguishable from other ligated double-stranded target nucleic acid molecules in the population." Guardant practices this element at least by attaching "library adapters containing inline barcodes" to the ends of fragments of cell-free DNA. FDA Summary No. P200010B at 6; *see* Oliver Zill, et al., *The Landscape of Actionable Genomic Alterations in Cell-Free Circulating Tumor DNA from 21,807 Advanced Cancer Patients*, 24(15) Clin. Cancer Res. 3528-38 & Supp. (Aug. 1, 2018) ("Zill") (Exhibit K) (article authored by Guardant employees regarding Guardant's digital sequencing technology). Double-stranded cfDNA is

"labeled with oligonucleotide barcodes." Justin Odegaard, et al., *Validation of a Plasma-Based Comprehensive Cancer Genotyping Assay Utilizing Orthogonal Tissue- and Plasma-Based Methodologies*, 24(15) Clin. Cancer Res. 3539–49, at 3542, Fig. 1 (Apr. 24, 2018) ("Odegaard") (Exhibit L) (article authored by Guardant employees regarding Guardant's digital sequencing technology). After library preparation, enrichment, and sequencing, "[i]ndividual unique input molecules are then bioinformatically reconstructed using barcodes and sequence data to suppress analytic error modes." *Id*. Guardant "build[s] double-stranded consensus representations of original unique cfDNA molecules using both inferred molecular barcodes and read start/stop positions." *Id.* at 3540.

42. Guardant also practices the "strand-distinguishing nucleotide sequence" element of claim 1 of the '631 patent. This element recites "a strand-distinguishing nucleotide sequence that, following the ligation step, provides a region of non-complementarity between a first strand of each adapter-target nucleic acid complex and a second strand of the same adapter-target nucleic acid complex." Guardant practices this element at least by requiring "each single-stranded half of the original double-stranded 5-30 ng input cfDNA sample" to be "separately encoded with oligonucleotide heptamers to create a self-referenced digital sequence duplex library with properties similar to differential signaling in digital communications." *See* Lanman at 22, Fig. S2. "[N]on-unique oligonucleotide heptamer barcodes are ligated to each half of individual double-stranded cfDNA." *Id.* at 18. Guardant further practices this element at least by "generat[ing] a duplex library whereby each single-stranded half of the original double-stranded input cfDNA sample is separately encoded with said oligonucleotides." *Id.* Guardant also practices this element by having "[e]ach strand of a double-stranded cfDNA molecule . . .

individually tagged, allowing custom software to compare the two complementary strands . . . ." *See id.* at 19.

43. Guardant also practices the "amplifying" element of claim 1 of the '631 patent. This element recites "for each of the adapter-target nucleic acid complexes—amplifying each strand of the adapter-target nucleic acid complex to produce a plurality of first strand adapter-target nucleic acid complex amplicons and a plurality of second strand adapter-target nucleic acid complex amplicons." Guardant practices this element at least by performing a step where "in-line adapters are ligated immediately after cfDNA isolation, prior to PCR and target capture steps." Zill at 1; *see* FDA Summary No. P200010B at 6 (describing that the cfDNA fragments ligated to barcoded adapters are amplified by PCR before multiple samples are pooled for sequencing); *see* Lanman at 22, Fig. S2 (describing that after generating a duplex library, the digital sequence libraries are amplified).

44. Guardant also practices the "sequencing" element of claim 1 of the '631 patent. This element recites "sequencing the adapter-target nucleic acid complex amplicons to produce a plurality of first strand sequence reads and plurality of second strand sequence reads." Guardant practices this element at least by "parallel sequencing of amplified target genes to an average depth of coverage greater than 2,700 unique molecules." *See* FDA Summary No. P200010B at 6; *see* Lanman at 22, Fig. S2 (describing that the digital sequencing libraries are analyzed using paired-end sequencing).

45. Guardant also practices the "grouping" element of claim 1 of the '631 patent. This element recites "grouping the first strand sequence reads and the second strand sequence reads into a family of first and second strand sequence reads based on the degenerate or semi-degenerate SMI sequence alone or in combination with the target nucleic acid fragment ends."

Guardant practices this element at least by having "[e]ach strand of a double-stranded cfDNA molecule . . . individually tagged, allowing custom software to compare the two complementary strands . . . ." Lanman at 19. "Processed reads were then aligned to hg19 . . . and used to build double-stranded consensus representations of original unique cfDNA molecules using both inferred molecular barcodes and read start/stop positions." Odegaard at 3540. Moreover, Guardant practices this element at least by detecting fusions, whereby "overlapping paired-end reads [are] merged to form a representation of candidate fusion cfDNA molecules that are mapped to initial unique cfDNA molecules based on molecular barcoding and alignment information. Zill at 2. "Candidate fusion events are identified as clusters of molecules with similar directionality and breakpoint proximity . . . ." *Id.*

46. Guardant also practices the "separating" element of claim 1 of the '631 patent. This element recites "separating the first and second strand sequence reads into a set of first strand sequence reads and a set of second strand sequence reads based on the region of non-complementarity between the first strand and the second strand of the adapter-target nucleic acid complex." Guardant practices this element at least by having "[e]ach strand of a double-stranded cfDNA molecule . . . individually tagged, allowing custom software to compare the two complementary strands . . . ." Lanman at 19.

47. Guardant also practices the "confirming" element of claim 1 of the '631 patent. This element recites "confirming the presence of at least one first strand sequence read and at least one second strand sequence read." Guardant practices this element at least by using sequencing reads "to reconstruct each individual cfDNA molecule present in the original patient sample with high-fidelity using proprietary double-stranded consensus sequence representation." Odegaard at 3542. Guardant also practices this element at least by "measur[ing] the total number

of unique fragments covering each gene comprised of both halves of the original parent molecules." Lanman at 19.

48. Guardant also practices the "comparing" element of claim 1 of the '631 patent. This element recites "comparing the at least one first strand sequence read with the at least one second strand sequence read." Guardant practices this element at least by comparing the two complementary and individually tagged strands of a cfDNA molecule to ascertain any errors. *See* Lanman at 18–19.

49. Guardant also practices the "non-complementary identifying" element of claim 1 of the '631 patent. This element recites "identifying nucleotide positions where the compared first and second strand sequence reads are non-complementary." Guardant practices this element at least by comparing the two complementary and individually tagged strands of a cfDNA molecule "to ascertain whether either has acquired an erroneous variant due to a sequencing error, library preparation error, or DNA damage during sample processing." Lanman at 19. Guardant further practices this element at least by "building a separate noise model for each and every one of the . . . bases," and at least by "compar[ing] the two complementary strands . . . ." *Id.*

50. Guardant also practices the "complementary identifying" element of claim 1 of the '631 patent. This element recites "identifying nucleotide positions where the compared first and second strand sequence reads are complementary." Guardant practices this element at least by requiring that, "[c]ritically, >50% of molecules are reconstructed from both strands of the original cfDNA molecule, greatly increasing consensus sequence fidelity and specificity . . . ." Odegaard at 3542. As discussed above, Guardant's former Chief Medical Officer described Guardant's products as barcoding each strand of DNA and finding agreement between the

complementary strands; if they do not match, Guardant corrects the sequencing. The Lung Cancer Living Room – Molecular Testing, Bonnie J. Addario Lung Cancer Foundation, YOUTUBE, 0:56:12–0:56:36 (Feb. 21, 2017).

51. Guardant also practices the "generating" element of claim 1 of the '631 patent. This element recites "generating a high accuracy consensus sequence read for each of the double-stranded target nucleic acid molecules in the population that includes only the nucleotide positions where the compared first and second strand sequence reads are complementary." Guardant practices this element at least by using sequencing reads to reconstruct "each individual cfDNA molecule present in the original patient sample with high-fidelity using proprietary double-stranded consensus sequence representation." Odegaard at 3542. Errors were reduced to one error per three million reconstructed molecule nucleotides. Guardant IPO Prospectus at 121. Moreover, Guardant practices this element at least by combining "barcoding technology" with "bioinformatics filtering of sequencing errors via statistical filtering of sequencing errors per-base-pair." Zill at 1.

52. It is also expected that discovery will likely reveal additional evidentiary support that Guardant performs the above limitations of the '631 patent.

53. Guardant: (i) has known or should have known of the '631 patent no later than January 22, 2020, the first time the '631 patent was cited during the prosecution of Guardant's patent applications, (ii) infringed the patent after acquiring that knowledge, and (iii) in doing so, knew or should have known that its actions constituted and continue to constitute infringement of the '631 patent.

54. Guardant could not have reasonably or subjectively believed that its actions do not constitute infringement of the '631 patent. Nor could Guardant reasonably or subjectively

believe that the ’631 patent is invalid. Guardant’s actions are egregious and beyond typical infringement. Guardant thus willfully infringes the ’631 patent.

55. By its actions, Guardant’s infringement of the ’631 patent has irreparably harmed TwinStrand and UW. Unless Guardant’s infringing acts are enjoined by this Court, TwinStrand and UW will continue to suffer additional irreparable injury. TwinStrand and UW have no adequate remedy at law.

56. By its actions, Guardant’s infringement of the ’631 patent has damaged and continues to damage TwinStrand and UW in an amount yet to be determined, of at least a reasonable royalty and/or lost profits that TwinStrand and UW would have made but for Guardant’s infringing acts.

COUNT II

(Infringement of U.S. Patent No. 10,689,699)

57. Plaintiffs re-allege and incorporate by reference Paragraphs 1–56 above, as if fully set forth herein.

58. The ’699 patent is generally directed to methods for analyzing circulating DNA. Claim 1 of the patent recites:

> A method, comprising:
>
> a) providing a population of circulating DNA molecules obtained from a bodily sample from a subject;
>
> b) converting the population of circulating DNA molecules into a population of non-uniquely tagged parent polynucleotides, wherein each of the non-uniquely tagged parent polynucleotides comprises (i) a sequence from a circulating DNA molecule of the population of circulating DNA molecules, and (ii) an identifier sequence comprising one or more polynucleotide barcodes, such that each non-uniquely tagged parent polynucleotide is substantially unique with respect to other non-uniquely tagged parent polynucleotides in the population;

c) amplifying the population of non-uniquely tagged parent polynucleotides to produce a corresponding population of amplified progeny polynucleotides;

d) sequencing at least a portion of the population of amplified progeny polynucleotides to produce a set of sequence reads;

e) grouping the sequence reads into families, each of the families comprising sequence reads comprising the same identifier sequence and having the same start and stop positions, whereby each of the families comprises sequence reads amplified from the same non-uniquely tagged parent polynucleotide; and

f) collapsing sequence reads in each family to yield a base call for each family corresponding to one or more genetic loci.

59. Guardant has infringed and continues to infringe at least claim 1 of the '699 patent pursuant to 35 U.S.C. § 271(a), literally or under the doctrine of equivalents, by performing the methods of the '699 patent in the United States.

60. Guardant practices the "providing" element of claim 1 of the '699 patent. This element recites "providing a population of circulating DNA molecules obtained from a bodily sample from a subject." Guardant practices this element by at least "extracting, processing, and sequencing" cell-free DNA (cfDNA). Odegaard at 3540. "Cell-Free DNA is extracted from 1.5 mL to 5 mL plasma . . .." Lanman at 18. Guardant practices this element at least by "utiliz[ing] circulating cell-free DNA (cfDNA) from plasma of peripheral whole blood." FDA Summary No. P200010B at 1.

61. Guardant also practices the "converting" element of claim 1 of the '699 patent. This element recites "converting the population of circulating DNA molecules into a population of non-uniquely tagged parent polynucleotides." Guardant practices this element at least by converting circulating cfDNA fragments to digital sequence libraries by ligating "non-unique oligonucleotide heptamer barcodes," thereby tagging them. *See* Lanman at 18; Odegaard at 3540.

62. Guardant also practices the "barcode" element of claim 1 of the '699 patent. This element recites "an identifier sequence comprising one or more polynucleotide barcodes." Guardant practices this element at least by attaching adapters containing inline barcodes to the ends of cfDNA fragments as part of their library preparation. *See* FDA Summary No. P200010B at 6. Cell-free DNA is "labeled with oligonucleotide barcodes at high efficiency." Odegaard at 3542, Fig. 1.

63. Guardant also practices the "substantially unique" element of claim 1 of the '699 patent. This element recites that "each non-uniquely tagged parent polynucleotide is substantially unique with respect to other non-uniquely tagged parent polynucleotides in the population." Guardant practices this element at least by labeling cfDNA "with nonrandom oligonucleotide adapters ('molecular barcodes')" and reconstructing "[i]ndividual unique input molecules . . . *using barcode and sequence data* . . . ." Odegaard at 3542, Fig. 1E (emphasis added).

64. Guardant also practices the "amplifying" element of claim 1 of the '699 patent. This element recites "amplifying the population of non-uniquely tagged parent polynucleotides to produce a corresponding population of amplified progeny polynucleotides." Guardant practices this element at least by amplifying these barcoded cfDNA fragments by PCR. FDA Summary No. P200010B at 6. After double-stranded cfDNA molecules are ligated to molecular barcodes, the "digital sequence libraries are amplified." Lanman at 22, Fig. S2.

65. Guardant also practices the "sequencing" element of claim 1 of the '699 patent. This element recites "sequencing at least a portion of the population of amplified progeny polynucleotides to produce a set of sequence reads." Guardant practices this element at least by the "parallel sequencing of amplified target genes to an average depth of coverage of greater than

2,700 unique molecules." FDA Summary No. P200010B at 6. *See* Lanman at 22, Fig. S2 (describing that the digital sequencing libraries are analyzed using paired-end sequencing).

66. Guardant also practices the "grouping" element of claim 1 of the '699 patent. This element recites "grouping the sequence reads into families." Guardant practices this element at least by creating sequencing libraries and using molecular tagging to identify particular sequences, and at least by noise filtering and molecular tracking where "[i]ndividual unique input molecules are then bioinformatically reconstructed using barcode and sequence data to suppress analytic error modes." *See* Odegaard at 3542, Fig. 1E. Also, Guardant practices this element at least by detecting candidate gene fusions whereby, "overlapping paired-end reads are merged to form a representation of candidate fusion cfDNA molecules that are mapped to initial unique cfDNA molecules based on molecular barcoding and alignment information." Zill at 2. "Candidate fusion events are identified as clusters of molecules with similar directionality and breakpoint proximity . . . and "[r]eference molecules are then constructed for each fusion candidate . . . ." *Id.*

67. Guardant also practices the "identifier sequence" element of claim 1 of the '699 patent. This element recites "each of the families comprising sequence reads comprising the same identifier sequence." Guardant practices this element at least by using "inferred molecular barcodes" and at least by noise filtering and molecular tracking where "[i]ndividual unique input molecules are then bioinformatically reconstructed using barcode and sequence data to suppress analytic error modes." *See* Odegaard at 3540, 3542, Fig. 1E.

68. Guardant also practices the "start/stop position" element of claim 1 of the '699 patent. This element recites sequence reads "having the same start and stop positions." Guardant practices this element at least by "build[ing] double-stranded consensus representations of

original unique cfDNA molecules" using barcodes and "read start/stop positions." Odegaard at 3540.

69. Guardant also practices the "non-uniquely tagged parent" element of claim 1 of the '699 patent. This element recites "each of the families comprises sequence reads amplified from the same non-uniquely tagged parent polynucleotide." Guardant practices this element at least by creating sequencing libraries from extracted cfDNA and at least by noise filtering and molecular tracking where "[i]ndividual unique input molecules are then bioinformatically reconstructed using barcode and sequence data to suppress analytic error modes." *See* Odegaard at 3542, Fig. 1E.

70. Guardant also practices the "collapsing" element of claim 1 of the '699 patent. This element recites "collapsing sequence reads in each family to yield a base call for each family corresponding to one or more genetic loci." Guardant practices this element at least by the step where "[i]ndividual unique input molecules are then bioinformatically reconstructed using barcode and sequence data to suppress analytic error modes." Odegaard at 3542, Fig. 1E. Additionally, Guardant practices this element at least by merging "overlapping paired-end reads . . . that are mapped to initial unique cfDNA molecules based on molecular barcoding and alignment information." Zill at 2. Moreover, Guardant's bioinformatics pipeline at least uses molecular barcoding technology for "reconstruct[ing] the original double-stranded cfDNA molecules present in a plasma sample, thereby transforming NGS read information into accurate, molecule-based variant calls." Zill at 1.

71. It is also expected that discovery will reveal additional evidentiary support that Guardant performs the above limitations of the '699 patent.

72. Guardant: (i) has known or should have known of the '699 patent no later than June 25, 2020, the first time the '699 patent was cited during the prosecution of Guardant's patent applications, (ii) infringed the patent after acquiring that knowledge, and (iii) in doing so, knew or should have known that its actions constituted and continue to constitute infringement of the '699 patent.

73. Guardant could not have reasonably or subjectively believed that its actions do not constitute infringement of the '699 patent. Nor could Guardant reasonably or subjectively believe that the '699 patent is invalid. Guardant's actions are egregious and beyond typical infringement. Guardant thus willfully infringes the '699 patent.

74. By its actions, Guardant's infringement of the '699 patent has irreparably harmed TwinStrand and UW. Unless Guardant's infringing acts are enjoined by this Court, TwinStrand and UW will continue to suffer additional irreparable injury. TwinStrand and UW have no adequate remedy at law.

75. By its actions, Guardant's infringement of the '699 patent has damaged and continues to damage TwinStrand and UW in an amount, yet to be determined, of at least a reasonable royalty and/or lost profits that TwinStrand and UW would have made but for Guardant's infringing acts.

COUNT III

(Infringement of U.S. Patent No. 10,752,951)

76. Plaintiffs re-allege and incorporate by reference Paragraphs 1–75 above, as if fully set forth herein.

77. The '951 patent is directed to methods of generating high accuracy sequence reads of a population of double-stranded target nucleic acid molecules. Claim 1 of the patent recites:

A method, comprising:

(a) providing a sample comprising a set of double-stranded polynucleotide molecules, each double-stranded polynucleotide molecule including first and second complementary strands;

(b) tagging said double-stranded polynucleotide molecules with a set of duplex tags;

(c) sequencing at least some of said tagged strands to produce a set of sequence reads;

(d) sorting sequence reads into paired sequence reads and unpaired sequence reads, wherein (i) each paired read corresponds to sequence reads generated from a first tagged strand and a second differently tagged complementary strand derived from an original parent polynucleotide molecule in said set, and (ii) each unpaired read represents a first tagged strand having no second differently tagged complementary strand derived from an original parent polynucleotide molecule represented among said sequence reads in said set of sequence reads; and

(e) quantifying at least two of (i) said paired sequence reads, (ii) said unpaired sequence reads, (iii) read depth of said paired sequence reads and (iv) read depth of said unpaired sequence reads.

78. Guardant has infringed and continues to infringe at least claim 1 of the ’951 patent pursuant to 35 U.S.C. § 271(a), literally or under the doctrine of equivalents, by performing the methods of the ’951 patent in the United States.

79. Guardant practices the “providing” element of claim 1 of the ’951 patent. This element recites “providing a sample comprising a set of double-stranded polynucleotide molecules, each double-stranded polynucleotide molecule including first and second complementary strands.” Guardant practices this element at least by “utiliz[ing] cell-free DNA (cfDNA) from plasma of peripheral whole blood.” FDA Summary No. P200010B at 1. “Isolated cfDNA fragments are subsequently converted to digital sequence libraries.” Lanman at 18.

80. Guardant also practices the “tagging” element of claim 1 of the ’951 patent. This element recites “tagging said double-stranded polynucleotide molecules with a set of duplex

tags." Guardant practices this element at least by performing a step where "cfDNA fragment ends are repaired and library adapters containing inline barcodes are attached using blunt-end ligation." FDA Summary No. P200010B at 6. Cell-free DNA is "extracted from stabilized whole blood, [and] labeled at high efficiency with nonrandom oligonucleotide adapters ('molecular barcodes')." Odegaard at 3542.

81. Guardant also practices the "sequencing" element of claim 1 of the '951 patent. This element recites "sequencing at least some of said tagged strands to produce a set of sequence reads." Guardant practices this element at least by performing steps where "adapters containing inline barcodes are attached" to the cfDNA and "[t]he resulting DNA is amplified by PCR" before "[p]aired-end sequencing by synthesis is performed with the Illumina NextSeq 550 Sequencing system." FDA Summary No. P200010B at 6.

82. Guardant also practices the "sorting" element of claim 1 of the '951 patent. This element recites "sorting sequence reads into paired sequence reads and unpaired sequence reads, ..." Guardant practices this element at least by sorting sequence reads into paired sequence reads and unpaired sequence reads and at least by "measur[ing] the total number of unique fragments covering each gene comprised of both halves of the original parent molecules" and identifying "uneven representation of each half of the original double-stranded library." Lanman at 19. "[T]he digital decoding process comprises analysis of both strands of each unique cfDNA molecule to greatly increase the accuracy." *Id.* at 19. "Critically, >50% of molecules are reconstructed from both strands of the original cfDNA molecule, greatly increasing consensus sequence fidelity and specificity over other previously published approaches." Odegaard at 3542.

83. Guardant also practices the "paired read" element of claim 1 of the '951 patent. This element recites "(i) each paired read corresponds to sequence reads generated from a first

tagged strand and a second differently tagged complementary strand derived from an original parent polynucleotide molecule in said set, ...” Guardant practices this element at least by performing the step where “[e]ach strand of a double-stranded cfDNA molecule is individually tagged, allowing custom software to compare the two complementary strands” and at least by “measur[ing] the total number of unique fragments covering each gene comprised of both halves of the original parent molecules.” Lanman at 19; *see also* Odegaard at 3540–41. “[T]he digital decoding process comprises analysis of both strands of each unique cfDNA molecule to greatly increase accuracy.” Lanman at 19. “Critically, >50% of molecules are reconstructed from both strands of the original cfDNA molecule, greatly increasing consensus sequence fidelity and specificity over other previously published approaches. Odegaard at 3542.

84. Guardant also practices the “unpaired read” element of claim 1 of the ’951 patent. This element recites “(ii) each unpaired read represents a first tagged strand having no second differently tagged complementary strand derived from an original parent polynucleotide molecule represented among said sequence reads in said set of sequence reads.” Guardant practices this element at least by sorting unpaired sequence reads representing a sequence read generated from a first tagged strand having no second differently tagged complementary strand. Odegaard at 3542; *see also* Lanman at 19. Guardant practices this element also at least by “measur[ing] the total number of unique fragments covering each gene comprised of both halves of the original parent molecules” and identifying “uneven representation of each half of the original double-stranded library.” Lanman at 19. “[T]he digital decoding process comprises analysis of both strands of each unique cfDNA molecule to greatly increase accuracy.” *Id.* “Critically, >50% of molecules are reconstructed from both strands of the original cfDNA

molecule, greatly increasing consensus sequence fidelity and specificity over other previously published approaches. Odegaard at 3542.

85. Guardant also practices the "quantifying" element of claim 1 of the '951 patent. This element recites "quantifying at least two of: . . . ." Guardant practices this element at least by quantifying reads by defining "SNV and indel cut-offs . . . in terms of mutant allele fraction (MAF) estimate, number and type of molecules supporting the alteration, pseudo-gene assessment, and likelihood ratio (LLR) score." FDA Summary No. P200010B at 7. Guardant also practices this element at least by "measur[ing] the total number of unique fragments covering each gene comprised of both halves of the original parent molecules" and identifying "uneven representation of each half of the original double-stranded library" and by "digital sequencing [that] enables tracking and quantification of all unique cfDNA fragments overlapping a given genomic site" Lanman at 18. "[T]he digital decoding process comprises analysis of both strands of each unique cfDNA molecule to greatly increase accuracy." *Id.* at 19. "Critically, >50% of molecules are reconstructed from both strands of the original cfDNA molecule, greatly increasing consensus sequence fidelity and specificity over other previously published approaches. Odegaard at 3542.

86. Guardant also practices the "paired sequence reads" element of claim 1 of the '951 patent. This element recites "(i) said paired sequence reads" Guardant practices this element at least by quantifying paired sequence reads (*e.g.*, by reconstructing the set of unique molecules in a set to calculate mutant allele fraction). Lanman at 18–19.

87. Guardant also practices the "unpaired sequence reads" element of claim 1 of the '951 patent. This element recites "(ii) said unpaired sequence reads." Guardant practices this element at least by quantifying unpaired sequence reads (*e.g.*, by calculating copy number

alterations). Lanman at 18–19. "[T]he digital decoding process comprises analysis of both strands of each unique cfDNA molecule to greatly increase accuracy." Lanman at 19. "Critically, >50% of molecules are reconstructed from both strands of the original cfDNA molecule, greatly increasing consensus sequence fidelity and specificity over other previously published approaches. Odegaard at 3542.

88. Guardant also practices the "paired read depth" element of claim 1 of the '951 patent. This element recites "(iii) read depth of said paired sequence reads." Guardant practices this element at least by quantifying the read depth of paired sequence reads. Odegaard at 3542. Guardant also practices this element at least by "parallel sequencing of amplified target genes to an average depth of coverage greater than 2,700 unique molecules." *See* FDA Summary No. P200010B at 6.

89. Guardant also practices the "unpaired read depth" element of claim 1 of the '951 patent. This element recites "(iv) read depth of said unpaired sequence reads." Guardant practices this element at least by quantifying the read depth of unpaired sequence reads. Odegaard at 3542. Guardant also practices this element at least by "parallel sequencing of amplified target genes to an average depth of coverage greater than 2,700 unique molecules." *See* FDA Summary No. P200010B at 6. "[T]he digital decoding process comprises analysis of both strands of each unique cfDNA molecule to greatly increase accuracy." Lanman at 19. "Critically, >50% of molecules are reconstructed from both strands of the original cfDNA molecule, greatly increasing consensus sequence fidelity and specificity over other previously published approaches. Odegaard at 3542.

90. It is also expected that discovery will likely reveal additional evidentiary support that Guardant performs the above limitations of the '951 patent.

91. Guardant: (i) has known or should have known of the '951 patent no later than the filing of this Complaint, (ii) infringed the patent after acquiring that knowledge, and (iii) in doing so, knew or should have known that its actions constituted and continue to constitute infringement of the '951 patent.

92. Guardant could not have reasonably or subjectively believed that its actions do not constitute infringement of the '951 patent. Nor could Guardant reasonably or subjectively believe that the '951 patent is invalid. Guardant's actions are egregious and beyond typical infringement. Guardant thus willfully infringes the '951 patent.

93. By its actions, Guardant's infringement of the '951 patent has irreparably harmed TwinStrand and UW. Unless Guardant's infringing acts are enjoined by this Court, TwinStrand and UW will continue to suffer additional irreparable injury. TwinStrand and UW have no adequate remedy at law.

94. By its actions, Guardant's infringement of the '951 patent has damaged and continues to damage TwinStrand and UW in an amount, yet to be determined, of at least a reasonable royalty and/or lost profits that TwinStrand and UW would have made but for Guardant's infringing acts.

COUNT IV

(Infringement of U.S. Patent No. 10,760,127)

95. Plaintiffs re-allege and incorporate by reference Paragraphs 1–94 above, as if fully set forth herein.

96. The '127 patent is generally directed to methods of sequencing DNA. Claim 1 of the patent recites:

A method of sequencing DNA comprising:

a) attaching adapters to double-stranded DNA fragments to generate a plurality of partially-complementary, asymmetrical double-stranded adapter-DNA molecules, wherein the adapters comprise barcodes selected from a plurality of distinct barcode sequences;

b) amplifying original strands of at least a portion of the double-stranded adapter-DNA molecules to produce first and second strand copies;

c) sequencing a plurality of first and second strand copies to obtain first and second strand sequence reads for at least a portion of the adapter-DNA molecules; and

d) for at least some of the adapter-DNA molecules comprising barcodes—

confirming the presence of at least one sequence read derived from each of the original first and second strands of the adapter-DNA molecules;

comparing at least one of the confirmed first and second strand sequence reads to a reference sequence; and

analyzing one or more correspondences between the at least one of the confirmed first and second strand sequence reads and the reference sequence to identify a sequence variation.

97. Guardant has infringed and continues to infringe at least claim 1 of the '127 patent pursuant to 35 U.S.C. § 271(a), literally or under the doctrine of equivalents, by performing the methods of the '127 patent in the United States.

98. Guardant practices the "attaching" element of claim 1 of the '127 patent. This element recites "attaching adapters to double-stranded DNA fragments to generate a plurality of partially-complementary, asymmetrical double-stranded adapter-DNA molecules." Guardant practices this element at least by performing a step where "cfDNA fragment ends are repaired and library adapters containing inline barcodes are attached using blunt-end ligation" and "amplified by PCR using a unique index primer." FDA Summary No. P200010B at 6. In addition, Guardant practices this element at least by "generat[ing] a duplex library whereby each single-stranded half of the original double-stranded input cfDNA sample is separately encoded with [complementary heptamer] oligonucleotides." Lanman at 18; *see also* Odegaard at 3542.

99. Guardant also practices the "barcode" element of claim 1 of the '127 patent. This element recites "wherein the adapters comprise barcodes selected from a plurality of distinct barcode sequences." Guardant practices this element at least by performing a step of "molecular barcoding (in-line adapters are ligated immediately after cfDNA isolation, prior to PCR and target capture steps)." Zill at 1. Cell-free DNA is "labeled at high efficiency with nonrandom oligonucleotide adapters ('molecular barcodes')." Odegaard at 3542.

100. Guardant also practices the "amplifying" element of claim 1 of the '127 patent. This element recites "amplifying original strands of at least a portion of the double-stranded adapter-DNA molecules to produce first and second strand copies." Guardant practices this element at least by performing the step where "[t]he resulting DNA is amplified by PCR to create libraries suitable for enrichment." FDA Summary No. P200010B at 6. After double-stranded cfDNA molecules are ligated to molecular barcodes, the "digital sequence libraries are amplified." Lanman at 22, Fig. S2.

101. Guardant also practices the "sequencing" element of claim 1 of the '127 patent. This element recites "sequencing a plurality of first and second strand copies to obtain first and second strand sequence reads for at least a portion of the adapter-DNA molecules." Guardant practices this element at least by performing a step where "[p]aired-end sequencing by synthesis is performed with the Illumina NextSeq 550 Sequencing system," before "execut[ing] a proprietary algorithmic reconstruction of the digitized sequencing signals based on molecular barcodes" on both first and second strand sequences. FDA Summary No. P200010B at 6.

102. Guardant also practices the "confirming" element of claim 1 of the '127 patent. This element recites "for at least some of the adapter-DNA molecules comprising barcodes—confirming the presence of at least one sequence read derived from each of the original first and

second strands of the adapter-DNA molecules." Guardant practices this element at least by confirming the presence of reads from "both strands of each" adapter-DNA molecule. Lanman at 18–19.

103. Guardant also practices the "comparing" element of claim 1 of the '127 patent. This element recites "comparing at least one of the confirmed first and second strand sequence reads to a reference sequence." Guardant practices this element at least by performing a step where "[t]he sequence data then undergoes an alignment process where it is mapped to the human genome (hg19) and an analysis of sequence alteration data is performed." FDA Summary No. P200010B at 6*; see also* Lanman at 18–19. "Processed reads [are] then aligned to hg19 [reference genome] . . .." Odegaard at 3540.

104. Guardant also practices the "analyzing" element of claim 1 of the '127 patent. This element recites "analyzing one or more correspondences between the at least one of the confirmed first and second strand sequence reads and the reference sequence to identify a sequence variation." Guardant practices this element at least by performing a step where "[p]rocessed reads [are] then aligned to hg19 . . . and used to build double-stranded consensus representations of original unique cfDNA molecules . . . ," which are used for variant "detect[ion] by comparing read and consensus molecule characteristics to sequencing platform- and position-specific reference error noise profiles." Odegaard at 3540–41. Guardant also practices this element at least by performing a step where "[t]he sequence data then undergoes an alignment process where it is mapped to the human genome (hg19) and an analysis of sequence alteration data is performed." FDA Summary No. P200010B at 6; *see also* Odegaard at 3540–41.

105. It is also expected that discovery will likely reveal additional evidentiary support that Guardant performs the above limitations of the '127 patent.

106. Guardant: (i) has known or should have known of the '127 patent no later than the filing of this Complaint—, (ii) infringed the patent after acquiring that knowledge, and (iii) in doing so, knew or should have known that its actions constituted and continue to constitute infringement of the '127 patent.

107. Guardant could not have reasonably or subjectively believed that its actions do not constitute infringement of the '127 patent. Nor could Guardant reasonably or subjectively believe that the '127 patent is invalid. Guardant's actions are egregious and beyond typical infringement. Guardant thus willfully infringes the '127 patent.

108. By its actions, Guardant's infringement of the '127 patent has irreparably harmed TwinStrand and UW. Unless Guardant's infringing acts are enjoined by this Court, TwinStrand and UW will continue to suffer additional irreparable injury. TwinStrand and UW have no adequate remedy at law.

109. By its actions, Guardant's infringement of the '127 patent has damaged and continues to damage TwinStrand and UW in an amount, yet to be determined, of at least a reasonable royalty and/or lost profits that TwinStrand and UW would have made but for Guardant's infringing acts.

JURY DEMAND

110. TwinStrand and the UW demand a jury trial on all issues so triable.

PRAYER FOR RELIEF

WHEREFORE, TwinStrand and UW respectfully request that this Court enter judgment against Guardant as follows:

A. That one or more claims of the '631 patent have been infringed by Guardant's use, offer for sale, and sale of its Accused Products and Accused Services;

B. That Guardant's infringement of the '631 patent has been willful;

C. That one or more claims of the ’699 patent have been infringed by Guardant’s use, offer for sale, and sale of its Accused Products and Accused Services;

D. That Guardant’s infringement of the ’699 patent has been willful;

E. That one or more claims of the ’951 patent have been infringed by Guardant’s use, offer for sale, and sale of its Accused Products and Accused Services;

F. That Guardant’s infringement of the ’951 patent has been willful;

G. That one or more claims of the ’127 patent have been infringed by Guardant’s use, offer for sale, and sale of its Accused Products and Accused Services;

H. That Guardant’s infringement of the ’127 patent has been willful;

I. An award of damages adequate to compensate TwinStrand and UW for the patent infringements that have occurred, together with pre-judgment interest and costs;

J. An accounting for acts of infringement not presented at trial and/or up to the judgment and an award by the Court of additional damage for any such acts of infringement;

K. A permanent injunction against Guardant, its affiliates, subsidiaries, officers, directors, agents, employees, and those persons in active concert on participation with any of them, from further infringement, or alternatively, award an ongoing royalty for Guardant’s post-verdict infringement, payable on each product or service offered by Guardant that is found to infringe one or more of the patents asserted herein, and on all future products and services that are not colorably different from those found to infringe;

L. An award of all other damages permitted by 35 U.S.C. § 284, including increased damages of three times the amount of compensatory damages found;

M. A judgment that this case is an exceptional case under 35 U.S.C. § 285 and an award of attorneys' fees incurred in this action;

N. An award of UW's and TwinStrand's costs and expenses in this action; and

O. Such other relief, including other monetary and equitable relief, as this Court deems just and proper.

Dated: August 3, 2021

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